Rethinking Clinical Trials (REaCT) Program – an example of a Pragmatic Trials program at OHRI

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Objectives

• Why is clinical trial accrual so low?
• Why do we have so many standard of care interventions – but no "standard"?
• Pragmatic clinical trials
• Ottawa REthinking Clinical Trials (REaCT) Program

Conflict of interest / Why am I speaking?

• Professional
  • I am a medical oncologist
  • I speak to patients and their families everyday
• Research
  • PI and co-I on many trials
  • I have presented to many REBs
  • I have patient advocates and methodologists in on the design of trials
• Regulatory
  • I sat on the Sunnybrook REB for 5 years
  • I enjoy contacting Health Canada
• Personal
  • I am a health care user – epilepsy, cancer, dementia
  • I have received care based on a cluster randomised trial results

Walk a mile in her shoes

I think Erika got good care
But did she get the best care?
We are all responsible for ensuring that research happens and that it changes practice

There is no more neutrality in the world.
You either have to be part of the solution, or you're going to be part of the problem.

Elridge Cleaver

Less the 3% of cancer patients go on a trial!

Canadian Partnership Against Cancer 2015
Why is accrual to trials so low?

- Challenges of traditional clinical trials
  - Ave. Cost: $26,000/patient
  - Physician engagement
  - Written consent process
  - Ethic board submission
  - Contracts
  - Superfluous data collection
  - Patient engagement
  - Research coordination/management
  - High drug costs

Barriers: physician, patient, protocol, institutional and regulatory

Why do we have so many standard of care interventions?

- Current clinical trials model is focused on:
  - developing new agents where many others already exist
  - or new indications for older agents

- Slow and expensive (and self perpetuating)

- Very few patients go on them
  - Patients highly selected
  - It’s getting worse – aging population, more drugs

- Once funded there is no commercial interest in supporting trials of fully funded agents.

Currently

- We have:
  - Increasing number of cancer patients
  - Expanding knowledge about cancer
  - Increasing number of treatments
  - Growth of cancer budgets

- Paradoxically, despite this we do not have guidance for many areas of care that impact on:
  - Patient cancer outcomes
  - Patient quality of life
  - Healthcare system sustainability

In clinical practice a physician is often faced with multiple potential treatment options without evidence of their comparative effectiveness and costs

- Want to identify treatments
  - Where benefits > harms
  - Where harms > benefits
  - That do not work

http://clinicalevidence.bmj.com/x/set/static/cms/efficacy-categorisations.html

A simple example, when I see a patient with breast cancer

- Over 10 fully funded chemotherapy regimens.
- All of which could be considered standard of care and “reasonable”.
- But very different:
  - toxicity profiles
  - direct drug costs to the pt & health care system.
- But without ever knowing which is the best!

So what’s the solution?

- Continue doing what we’ve always done
- Re-shuffling the pack – still the same cards
- Perhaps some extra money for a while
- It is easy to blame everyone and everything for poor trial accrual
- Look at the traditional model with fresh eyes

http://clinicalpractice.bmj.com/jon/doi/10.1136/clinpractice-2016-207360

What are pragmatic trials?

- A randomised controlled trial whose purpose is to inform decisions about practice.


What is the Rethinking Clinical Trials (REaCT) Program?

- Since 2014 repeated meetings with people in Ottawa who have not traditionally been involved in cancer trials.
- Questions around:
  - The traditional trials model
  - What can we learn from non-cancer trials?

The first thing we did was look at the current model!

Pragmatic trials initiative – 8 items

- Regular formal team feedback
- Selection of clinically relevant and practical questions
- Demonstration of clinical equipoise through surveys of knowledge users and systematic reviews
- Appropriate study design and simply defined study endpoints
- Written consent waived, integrated consent model
- Efficient Research Ethics Board (REB) approval
- Web-based randomization in the clinic
- Real-time easy electronic data capture and management
- A simple example, what dose and how many days of filgrastim do patients need?

- Filgrastim is used with nearly all adjuvant breast cancer regimens.
- We do not know the optimal dose - 480mcg $307.87 or 300mcg $192.42
- There is no limit on the number of days I can prescribe!
- What is standard of care?
- We did a survey of medical oncologists
  - everyone is doing “what they think is right”: 5, 7, 10 days
- We did a systematic review
  - Poor evidence, hence no evidence-based guidelines!
- Massive differences in costs to both patients and the Health Care System

Members

- Redrapa Thaworn (Economic analyst)
- Sasha Mazzarello (CRC)
- Mark Demons
- Brian Hutton
- Vanessa Lykerson- Dupre (Program Analyst)
- Dong Vo (Network Services Manager)
- Lisa Vandermeer
- Carol Stober (CRA)
- Dean Ferguson
- Tim Ramsay (Statistician)
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REaCT Trial Ideas: Topic Selection

- **Is the idea/question novel & innovative?**
  - Current funding means that there is no incentive for physicians or manufacturer to find out which is the correct dose

- **Is the question relevant and important?**
  - These injections hurt patients!
  - Massive expense (10 days [$24K] vs. 5 [$12K])

- **Will it broadly impact care and patient outcomes?**
  - Yes

### React-G Study

- **Feasibility endpoints**
  - Physician and patient engagement
  - Time for local or Provincial (Ontario Research Ethics Board, OCREB) approval
  - Patient/physician compliance

- **Secondary endpoints**
  - Rate of FN
  - Hospital admissions
  - Percentage of patients who require dose reductions/delays
  - Neutrophil counts at the end of each cycle of chemotherapy

### REaCT-G

- Patients for neo-adjuvant FEC-D, AC-D, AC-T, TC or VAC
- Consent template discussed with patient
- Oral consent
- Randomization
- Filgrastim 5 days
- Filgrastim 7 days
- Filgrastim 10 days
- Patient/physician treatment compliance
- Incidence of febrile neutropenia and hospitalization
- Real-time data collection

### REaCT-G concept

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### REaCT Trial Ideas: Topic Selection

- **Is it feasible?**
  - Thousands of women receive chemotherapy
  - Processes for filgrastim funding and administration are all in place

- **Do you find it interesting?**
  - If I don’t do this trial, will anyone else?
  - Minimal interest in funding the trial from CCO

### Efficient REB and regulatory processes

- REaCT trials MUST come within an ethical and moral framework.
- Proactive communication with REB for their input.
- Many very useful conversations with Health Canada by email and phone
Efficient consent processes

- Some realities!

- Despite our best efforts patients don’t read consent forms

- So when a major part of REB review is playing with punctuation — what are you achieving?

Oh – you don’t believe me?

- You are on a research week – the consent form is amazingly important!!!

- A signed consent form is not consent!

- Okay, what happens when the following appears on your; iphone, ipad whatever?

What do you do next? And you don’t have cancer


REaCT-G

Patients for non-hodgkin: FG, D, A, G, A, C, T, C, or TAC

Consent template discussed with patient

Oral consent

Randomization

Follow-up: 3 days, 7 days, 30 days

- Patients/physician treatment compliance
- Incidence of moderate neuropenia and hospitalization

Real-time data collection
Web-based randomization in the clinic

- Randomize eligible and consented patients in the clinic with either a mobile device or on desktop.

- Website includes:
  - a checklist of eligibility criteria
  - reminds the physician to dictate into EMR.

Web-based randomization in the clinic

- Randomization by either the physician or clinical research personnel

Email to physician when the patient next comes to clinic — data capture

Oversight and Monitoring

- Oversight of trials every 6-8 weeks
- Quarterly meeting; trial status, upcoming trials; action items; potential grants/leverage opportunities
- On-site monitoring visits every 3-8 months
- Ad hoc meeting to discuss trial results
- Twice a year retreat

REaCT-G

- Randomized: 140
  - Ottawa: 99
  - Kingston: 30
  - Kitchener: 11
- Withdrawn: 21/140 (15%)

React-G Study

- Feasible would be deemed successful if over 50% of appropriate patients approached agree to participate in the randomized trial
- At last analysis: 91% of pts agreed to randomization
- and if over 50% of physicians who agree at study commencement to participate in the study do indeed approach patients for the study
- 7/10 docs have approached patients, 6/10 docs have randomized pts
REaCT-G2

- With the demonstration of feasibility we are now expanded the study to demonstrate efficacy

Primary Outcome
- Rates of documented febrile neutropenia
- Rates of hospitalization

Secondary outcome
- Chemotherapy dose reductions, delays and discontinuations
- Sample size: 280 patients

Our current mandate

- To compare fully funded anti-cancer agents (e.g. drugs, radiotherapy, surgery)
- To provide practical guidance for care
- To improve patient care
- To reduce health care disparities
- To “save” health care dollars
- To challenge current research “processes” within an ethical framework

Current Clinical Trials

- Antibiotics or G-CSF for primary prophylaxis of febrile neutropenia?
- Duration of filgrastim primary prophylaxis
- Mg replacement
- Frequency of ejection fraction with trastuzumab
- PICC vs. PORT for trastuzumab-based chemotherapy
- PICC vs. peripheral access for non-trastuzumab-based adjuvant chemotherapy
- Type of chemo in early stage TNBC
- Dose Magee test effect time to start adjuvant therapy?
- Frequency of bone agents for MBC?
- So where are at?

So where are at?

- REaCT Accrual

Conclusion (1)

- <3% of cancer patients enrolled in prospective trials
- The clinical trials model is designed for development of new agents and new indications for old agents
- Not for comparisons of multiple “standards”
- Study populations – wealthy, Caucasian, highly educated, few co-morbidities, on few medications
- Not fair for patients, or society

Conclusion (2)

- REaCT is not perfect!
  - We will still need Phase 1, 2 and 3 trials
- Pragmatic, “cheap” model for answering practical questions
- We all need to be challenged – or YOU hindering research
- Expand out of oncology and beyond physicians
- An amazing opportunity for patient-centred collaboration
- Ottawa is leading the way!
Thanks

Key Assets/Partnerships

Ottawa Methods Centre
- Dean Fergusson
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External sites
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ICES@UOttawa
TOH Data Warehouse
TOH Performance Measurement
Knowledge Translation
Knowledge Synthesis

Devoted and responsive research administration
- awareness and investment in research facilitation/oversight/training

TOHs growing recognition and support of clinical research.